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Ab initio Molecular Dynamics of the Zn–Binding Site of the Alzheimer's Amyloid β–Peptide

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The aggregation of the peptide amyloid-β (Aβ) into fibrils is considered to be a key event in Alzheimer disease. Zn(II) ion binds the N-terminal segment of Aβ peptide (region 1-16) and influences its aggregation behaviour. Many experimental evidences revealed that Zn-binding involves the three histidine residues (6, 13 and 14). As for the fourth ligand, instead, different candidates have been proposed: Asp 1, Arg 5, Ser 8, Tyr 10 and Glu 11. Here we present the results obtained by *ab initio* molecular dynamics simulations (Car-Parrinello method) at 300 K of Zn(II)-Aβ(1-16) system and implications are discussed.

1 Introduction

In the Alzheimer's disease an accumulation of Aβ peptides occurs and fibrils are formed in the extracellular space of brain tissues. The reason of the accumulation is not known, but the amyloid precursor protein (APP) is probably involved in Cu transport. Other metal ions, like Zn, compete with Cu in APP binding: disfunction of metal ions homeostasis can be at the basis of the pathogenesys. Therefore, the investigation of the Cu and Zn binding sites in APP is important. Both Zn(II) and Cu(II) ions bind the N-terminal segment of Aβ peptide (region 1-16). Among the most recent and mostly debated experimental data, NMR results provided draft structures of Aβ(1-16)-Zn^{+2} complex in aqueous solution at pH=6.5[1] and the Zn binding involves as ligands His 6, His 13, His 14 imidazole groups and Glu 11 carboxylic group in tetrahedral coordination.

The identification of the fourth zinc ligand is extensively debated in literature: Asp 1, Arg 5, Ser 8, Tyr 10 and Val 12 have been also suggested as possible ligands participating in Cu^{+2} or Zn^{+2} chelation by Aβ[2]. The interplay between ligand flexibility and zinc quantum mechanics make the study of zinc coordination in Aβ(1-16) an ideal arena for *ab initio* Car-Parrinello[4] molecular dynamics (CPMD) simulation. The aim of our work is to model the structure of Aβ(1-16)-Zn^{+2}, indicating the fourth ligand.

2 Method

The starting system configurations for CPMD simulations were generated from random walk hybrid Monte Carlo trajectories[5] of a classical model of Aβ(1-16)Zn^{2+} system, employing the Amber force-field modified for possible candidate ligands. We chose four initial configurations with different fourth ligand: Glu 11, Asp 1 (bound to Zn by carboxyl groups), Tyr 10 and Ser 8 (bound by hydroxyl groups). CPMD simulations were made

using a parallel version of the Quantum-ESPRESSO package[3] which incorporates Vanderbilt ultrasoft pseudopotentials and Perdew–Burke–Ernzerhof exchange–correlation. After both electronic and atomic energy minimizations, the system was slowly heated up to 300 K and kept at this temperature for 1.6 ps of molecular dynamics simulation. Representative configurations have been optimized for detailed structural investigations.

3 Results and Discussion

Optimized configurations for the four Zn coordinations show that the three histidines (His 6, His 13, His 14) are bound to Zn. Only Ser 8 is displaced, as fourth ligand, by a backbone carbonyl group. By analysing the time evolution of Zn binding distances measured at 300 K we deduce that: in the single Asp 1 case, one histidine (His 13) is displaced from Zn, and this happens when Asp 7 carboxyl group deprotonates His 14 which then binds more strongly to Zn (distance oscillations in time are less wide). The binding of Zn by carboxyl groups (Asp 1 and Glu 11 cases) is stable. On the contrary, hydroxyl group (Tyr 10 case) binds Zn when assisted by hydrogen bond; as far as this hydrogen bond breaks, hydroxyl group is displaced by nearby peptide carbonyl group, as in the Ser 8 case minimization. Zn is almost always in a near tetrahedral coordination.

Zn-His binding is stable, except for His 13 in the very peculiar case of deprotonation of His 14 by Asp 7. Zn binding by hydroxyl groups of Tyr 10 is possible only when assisted by hydrogen bonds. In solution, the extent of water extrusion from the binding site (favouring intramolecular hydrogen bonds) can stabilize hydroxyl group as a fourth ligand. As far as carboxylic groups can approach Zn, they displace hydroxyl groups and eventual backbone carbonyl groups. This situation is expected to be different when Zn is replaced with Cu: the affinity of Cu for carboxylic and carbonyl groups is lower than that of Zn. Zn can displace Cu by the 1-16 portion of the chain, pushing Cu towards sites involving residues in different Aβ regions[2].

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